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PCT / IN 05 / 00055

INTELLECTUAL PROPERTY **INDIA**
PATENTS / DESIGNS / TRADE MARKS / GEOGRAPHICALINDICATION

सत्यमेव जयते

Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Application and Provisional Specification filed on 23/02/2004 in respect of Patent Application No.218/MUM/2004 of **M/S. CADILA HEALTHCARE LIMITED**, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Road, Ahmedabad – 380 015, Gujarat, India.

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act, 1970.

Dated this 26th day of May 2005.

(RAKESH KUMAR)
ASSTT.CONTROLLER OF PATENTS & DESIGNS.

ORIGINAL

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT
(See sections 5(2), 7, 54 and 135 and rule 33A)

1. We, **M/s Cadila Healthcare Limited**, a company incorporated under the Companies Act, 1956, of Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

2. Hereby declare-

   a) That we are in possession of an invention titled
   "An improved process for the manufacture of optically pure (R) or (S)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide."

   b) That the provisional specification relating to this invention is filed with this application.

   c) That there is no lawful ground of objection to grant of a patent to us.

3. Further declare that the true and first inventors for the said invention are:

1)	***RAMOLIA, Dilipkumar, Chandubhai***	*(Indian Citizen)*
2)	***PATIL, Dnyaneshwar, Sitaram***	*(Indian Citizen)*
3)	***PATEL, Dharmeshkumar Arvindbhai***	*(Indian Citizen*
4)	***SHARMA, Rajiv, Kumar***	*(Indian Citizen)*
5)	***AGARWAL, Virendra Kumar***	*(Indian Citizen*

4. We, claim the priority from the application filed in convention countries, particulars of which are as follows: **NIL**

5. That we are the assignee or legal representatives of the true and first inventors.

6. That our address for service in India is as follows:

   M/s Subramaniam, Natraj & Associates
   Attorneys-At-Law
   E-556, Greater Kailash-II
   New Delhi - 110 048, India.

   Phone: +91 11 29215603, 29226012, 29216025
   Facsimile: +91 11 29226005
   Email: sna@vsnl.com

218/mum/2004
Dt. 23/2/04

7. Following declaration was given by the inventors:

RAMOLIA, Dilipkumar, Chandubhai an Indian Citizen of Cadila Healthcare Limited, Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

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PATIL, Dnyaneshwar, Sitaram, an Indian Citizen of Cadila Healthcare Limited, Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

PATEL, Dharmeshkumar Arvindbhai, an Indian Citizen of Cadila Healthcare Limited, Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

SHARMA, Rajivkumar, an Indian Citizen of Cadila Healthcare Limited, Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

AGARWAL, Virendra Kumar, an Indian Citizen of Cadila Healthcare Limited, Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat India.

We, the true and first inventors for this application, declare that the applicants herein are our assignee:

RAMOLIA, Dilipkumar, Chandubhai

PATIL, Dnyaneshwar, Sitaram

PATEL, Dharmeshkumar Arvindbhai

SHARMA, Rajivkumar

AGARWAL, Virendra Kumar

8. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

9. Following are the attachment with the application:
   a) Provisional specification (3 copies)
   b) Application form 1 in triplicate.
   c) Statement and undertaking in FORM-3.
   d) Abstract.

Fee Rs._____ /- in Cash/ Cheque/ bank draft bearing No. _____ date _____ on _____ Bank.

We request that a patent may be granted to us for the said invention.

To,
The Controller of Patents
The Patent Office
At Mumbai

Date: 19-2-2004

Signature: _____
Name: Arun Parikh
Designation: Sr. Vice President
For **Cadila Healthcare Limited**

FORM 2

The PATENT ACT, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION

"AN IMPROVED PROCESS FOR THE MANUFACTURE OF OPTICALLY PURE (R) OR (S)-5-(2-AMINOPROPYL)-2-METHOXYBENZENESULFONAMIDE"

ORIGINAL

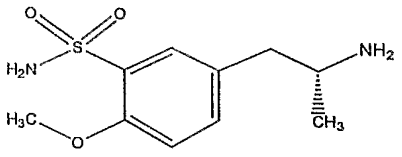
CADILA HEALTHCARE LIMITED, Zydus Tower, Satellite Cross Road, Ahmedabad, 380 015, Gujarat, India.

The present invention describes the nature of the invention:

FIELD OF INVENTION:

The present invention relates to an improved process for the manufacturing of a highly optical pure (R)-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide (Chiral purity: >99.9%) of formula I, which is a key intermediate for the preparation of Tamsulosin having formula II (EP-34432, US-4703063) useful in the treatment of patients with symptomatic Benign Prostatic Hyperplasia (BPH).

The present invention relates to a further simplified process for the preparation of enantiomerically pure methoxy benzenesulfonamide with D-(-) or L-(+)-tartaric acid as described in PCT/IN02/00244; filed on 26th December 2002 by Cadila Healthcare Ltd.



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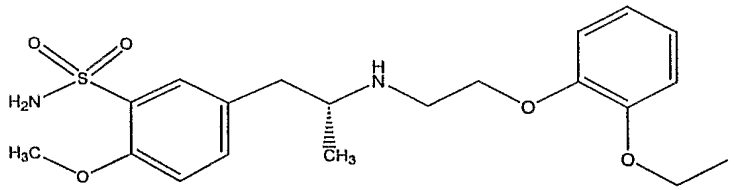


II

BACKGROUND OF THE INVENTION:

Tamsulosin is a selective blocker of α_{1C} –receptors, which shows a selective effect during treatment of problems related to hyperplasic prostate without influencing blood pressure or heart action (Honda K. and Nakagawa C.: α_1-adrenoceptor antagonist effect of optical isomer YM-12617 in rabbit lower urinary tract and prostate- J. Pharma. Exp. Ther.239, 512, (1986)).

The group of compounds as described in EP 34 432 are characterised by their ability to block α–adrenergic receptors, which led to their use in treating a number of diseases, especially, hypertension, congestive heart failure or problems related to the urinary tract.

This leads to the effort to effectively synthesize the optically active R-(-)-5-(2-aminopropyl)-2-methoxy benzenesulfonamide, which is the key intermediate of Tamsulosin. The PCT Application No.: PCT/IN02/00244

presented a synthesis of R-(-)-5-(2-aminopropyl)-2-methoxy benzenesulfonamide from the reduction of 5-(2-Hydroxyiminopropyl)-2-methoxy benzenesulfonamide followed by optical resolution of (R,S)-5-(2-amino propyl)-2-methoxy benzenesulfonamide with D-(-)-tartaric acid.

OBJECTS OF THE INVENTION:

In continuation of our work, we have adopted the kinetic resolution technique to resolve (R,S)-5-(2-amino-propyl)-2-methoxy benzenesulfonamide into R-(-)-5-(2-aminopropyl)-2-methoxy benzenesulfonamide and S-(+)-5-(2-aminopropyl)-2-methoxy benzenesulfonamide using D-(-) or L-(+)-tartaric acid as cheap resolving agent. Thus, the present invention provides a more commercially viable process.

Accordingly, it is an object of the present invention to provide a plant friendly and commercially viable process for the manufacture of R-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide (I). The objective of the present invention can only be achieved, if one can invent a suitable process for reacting exploiting a suitable solvent system at an appropriate temperature range with diastereomeric salt of (R,S)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide, wherein the differential solubility properties of the two can be used to obtain desired optically pure (R)-(-)-5-(2- aminopropyl)-2-methoxybenzenesulfonamide (I) in minimum possible operations.

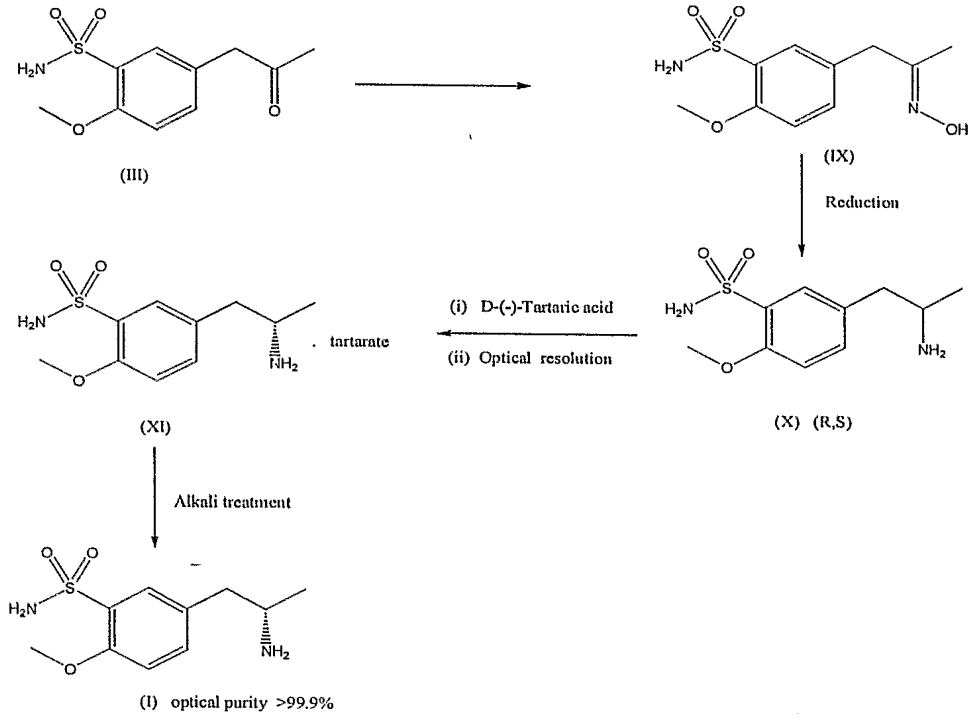
DETAILED DESCRIPTION:

Accordingly, the present invention provides a simplified process for the manufacture of optically pure (R) or (S)-5-(2- aminopropyl)-2-methoxybenzene sulfonamide (I), comprising resolution of (R,S)-5-(2-aminopropyl)-2-methoxybenzene-sulfonamide with D-(-) or L-(+)-tartaric to form a mixture of diastereomeric salts, separating the diastereomeric salts in a mixture of solvent systems of the kind such as described herein at a specified temperature range. The diastereomeric salt thus obtained is kinetically resolved two times in a same solvent system and under similar operational conditions to get desired

optical purity (> 99.9%). The purified diastereomeric salt is then basified to generate free (R)-(-)-5-(2-amino- propyl)-2-methoxybenzenesulfonamide (I) (Scheme - 1).

The molar ratio of (R, S)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide to the D-(-)-tartaric acid is 1:1 to 1:1.5, preferably 1:1.1. The diastereomeric salt formation as well as resolution is preferably carried out in a same solvent or the mixture of solvent system.

It has been observed that the resolution of (R,S)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide with D-(-)-tartaric acid is largely governed by the polarity of the solvent system used. The solvent system preferred is a combination of alcoholic solvents such as methanol, ethanol, 1-propanol and 2-propanol with 0-80%(v/v) of dipolar solvents such as N,N-dimethylformamide, N,N,-dimethylacetamide, N-methyl-2-pyrrolidone; dimethylsulfoxide or water. Though water alone can also be used for salt formation as well as resolution at ambient temperature, however in order to obtain optimum yield and optical purity, it is used in the combination with



Scheme-1

alcoholic solvents.

Temperature also plays a key role in kinetic resolution for obtaining the optically pure (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide. It has been also observed that if the resolution is carried out at 10-75°C temperature, the desired product is obtained in a higher optical purity. Thus the temperature between 30-65°C range provides the best results.

The reaction time may also vary between 0.1 to 26 hrs after the addition of the amine to the tartaric acid; however under optimal reaction conditions, the preferred reaction time is 4- 8 hrs to obtain the optimum yield with desired optical purity.

The separated diastereomeric salt (R:2S,3S) from the reaction mass is isolated by filtration. Moderately resolved diastereomeric salt may also be further purified twice using the same solvent system, under similar operational conditions. The purified salt is then treated with a base, i.e. alkali hydroxides, carbonates and hydrogen carbonates, preferably sodium hydroxide to bring pH 9.5-10.0 to obtain (R)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide as free base.

The mother liquor obtained from Ist and IInd crystallization contains 70-85% R-isomer of 5-(2-aminopropyl)-2-methoxybenzenesulfonamide as tartarate salt, that can be mixed in another batch during Ist purification to enhance the productivity. The resolving agent D-(-)-tartaric acid can be recovered from the aqueous mother liquor by usual known methods, as reported in literature and reused for the same resolution.

Besides D-(-)-tartaric acid, L-(+)-tartaric acid may also be used as a resolving agent. The resolution of (R,S)-5-(2-aminopropyl)-2-methoxybenzenesulfonamde using L-(+)-tartaric acid is also carried out in the same fashion. However in this case, (S:2R,3R) diastereomeric salt separates out from the reaction mixture which after desalting gives the S-(+)-5-(2-aminopropyl)-2-methoxy benzene sulfonamide.

In a preferred embodiment, (R,S)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide is treated with 1.1 molar ratio of D-(-)-tartaric acid in 8.5 volumes of methanol and 1.7 volumes of dimethylformamide with that of (R,S)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide at 60-65°C for 6 hours. The obtained solid is filtered at 60-65°C. The cake is slurrified with 3.0 volume of methanol, filtered and washed with 0.25 volumes of methanol. The wet product thus obtained is dried at 50–55°C till constant weight to give 70-75% yield of diastereomeric salt cotaining R-isomer 84-87% and S-isomer 13-16% as determined on chiral HPLC.

The obtained salt is refluxed in 6.5 volumes of aqueous methanol containing 38.5% (v/v) water with that of tartrate salt used for1 hour, then cooled to 40-45°C and maintained the same temperature for another 2 hours. The resulting mass is further cooled to 30-35°C and aged for 6 hours at same temperature range. The obtained solid is filtered and washed twice with 0.25 volumes of methanol with that of tartarate salt. The salt is dried at 50–55°C till constant weight to give 65-70% yield of purified diastereomeric salt containing R-isomer 98-99% and S-isomer 1-2% as determined on chiral HPLC.

The above obtained purified salt is again refluxed in 6.5 volumes of aqueous methanol containing 38.5% (v/v) water with that of tartrate salt used for 1 hour, then cooled to 40-45°C and maintained this temperature for 2 hours. The resulting mass is further cooled to 30-35°C and aged for 6 hours at same temperature range. The solid is filtered and then washed twice with 0.25 volumes of methanol with that of the tartarate salt. The salt is dried at 50–55°C till constant weight to give 65-70% yield of diastereomeric salt containing R-isomer 99.90-99.95% and S-isomer 0.05-0.10% as determined on chiral HPLC.

The present invention describes a simple methodology to get first moderately resolved tartarate salt of (R,S)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide, which on subsequent two simple purifications with same solvent system provides a diastereomeric salt with high optical purity i.e. more than 99.9%.

The present invention provides a highly optical pure (>99.9%) 5-(2-aminopropyl)-2-methoxybenzenesulfonamide with overall yield of 33-35% (without recyclable crop) from (R,S) 5-(2-aminopropyl)-2-methoxybenzene sulfonamide. The present method is also capable to reduce S-isomer from 50% to less than 0.05% thereby increasing the optical purity of R-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide from 50.0% to 99.95% exhibiting a successful kinetic resolution of diastereoisomeric salt.

The present invention is further described in greater detail as illustrated in number of examples.

Resolution of (R,S)-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide:

Example : 1. (TML/042/141)

Resolution of (R,S)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide

300.0 g (R,S)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide was added in 3000 ml of methanol : water mixture (95:5 % v/v) and then heated to 60-65°C for complete dissolution. 202.9 g of D-(-)-tartaric acid was slowly added at 60-65°C in the reaction mixture and then maintained 60-65°C temperature for 6 hours. The crystals were collected by filtration at same temperature (60-65°C), washed with 2 x 75 ml methanol and dried at 65-75°C temperature till constant weight to provide 187.3 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide tartarate.

Yield: 77.46 %

Melting point: 194-5°C (dec.)

$[\alpha]_D^{25}$: -19.4^0 (c = 1.0 , H_2O)

Example : 2. (TML/028/109)

Resolution of (R,S)-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide

250 g of (R,S)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide was added in 2550 ml of methanol : dimethyl formamide mixture (80:20 % v/v) then heated to 60-65°C for complete dissolution. 169 g of D-(-)-tartaric acid

was slowly added at 60-65°C in the reaction mixture and then maintained 60-65°C temperature for 6 hours. The crystals were filtered off. The wet product was taken in 750 ml of methanol and stirred for half an hour, at ambient temperature, was filtered off and washed with 2 x 62.5 ml methanol, thereby affording 193.3 g. of R-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide tartarate.

Yield: 95.92 %

Melting point: 193-4 °C(dec.)

$[\alpha]_D^{25}$: -19.16^0 (c = 1.0 , H_2O)

Ist Purification of R-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide tartarate

Example: 3 (TML/077/196)

[A] A mixture of 100 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide tartarate (obtained in Example-2), 400 ml methanol and 250 ml water was refluxed for 1 hour. The clear solution was slowly cooled to 40-45°C and maintained for 2 hours at 40-45°C. The reaction mass further cooled to 28-30°C and stirred for 6 hours at same temperature. The product was filtered at same temperature and washed with 2 x 25 ml methanol, dried the solid at 50-55°C till constant weight to give 63.3 g of R-(-)-5-(2-aminopropyl)-2-methoxy benzene sulfonamide tartarate.[ee : 98.38 %].

(TML/077/200)

[B] A mixture of 20 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide tartarate (obtained in Example-2), 160 ml methanol and 60 ml water was refluxed for 1 hour. The clear solution was slowly cooled to 40-45°C and maintained at 40-45°C for 2 hours. The reaction mass further cooled to 28-30°C and stirred for 6 hours at same temperature The product was filtered at same temperature and washed with 2 x 5 ml methanol, dried the solid at 50-55°C till constant weight to give 11.1 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide tartarate.[ee : 98.02 %].

(TML/091/042)

[C] A mixture of 97.0 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide tartarate (obtained in Example-2), 388 ml methanol and 170 ml water was refluxed for 1 hour. The clear solution was slowly cooled to 45-48°C and maintained at 45-48°C for 2 hours. The reaction mass further cooled to 28-30°C and stirred for 6 hours at same temperature. The product was filtered at same temperature and washed with 2 x 24 ml methanol, dried the solid at 50-55°C till constant weight to give 67.7 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide tartarate.[ee : 96.89 %].

(TML/091/043)

[D] A mixture of 101.0 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide tartarate (obtained in Example-2), 404 ml methanol and 202 ml water was refluxed for 1 hour. The clear solution was cooled to 45-47°C and maintained at 45-47°C for 2 hours. The reaction mass further cooled to 28-30°C and stirred for 6 hours at same temperature. The product was filtered at same temperature and washed with 2 x 25 ml methanol, dried the solid at 50-55°C till constant weight to give 64.0 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide tartarate having ee = 97-97.5 %.

Example: 4

IInd Purification of R-(-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide tartarate

(TML/091/035)

[A] A mixture of 56.0 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide tartarate (obtained in Example-3A), 224 ml methanol and 140 ml water was refluxed for 1 hour. The clear solution was slowly cooled to 40-45°C and maintained at 40-45°C for 2 hours. The reaction mass further cooled to 28-30°C and stirred for 6 hours at same temperature. The product was filtered

at same temperature and washed with 2 x 14 ml methanol, dried the solid at 50-55°C till constant weight to give 40.7 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide tartarate having ee = 99.98-100.0 %.

(TML/091/044)

[B] A mixture of 63.0 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide tartarate (obtained in Example-3C), 252 ml methanol and 110.2 ml water was refluxed for 1 hour. The clear solution was slowly cooled to 50-55°C and maintained at 50-55°C for 2 hours. The reaction mass further cooled to 28-30°C and stirred for 6 hours at same temperature. The product was filtered at same temperature and washed with 2 x 15 ml methanol, dried the solid at 50-55°C till constant weight to give 49.6 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide tartarate having ee = 99.40-99.70 %.

(TML/091/045)

[C] A mixture of 59.0 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide tartarate (obtained in Example-3D), 236 ml methanol and 118 ml water was refluxed for 1 hour. The clear solution was slowly cooled to 50-55°C and maintained at 50-55°C for 2 hours. The reaction mass further cooled to 28-30°C and stirred for 6 hours at same temperature. The product was filtered at same temperature and washed with 2 x 14 ml methanol, dried the solid at 50-55°C till constant weight to give 44.7 g of R-(-)-5-(2-aminopropyl)-2-methoxybenzene sulfonamide tartarate tartarate having ee = 99.40-99.60 %.

Example : 5

Preparation of R- (-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide

To 10 g tartarate salt (obtained in Eexample-4A) of R-(-)-5-(2-aminopropyl) -2-methoxybenzene sulfonamide in 10 ml water was added 40% aq. sodium hydroxide solution, to adjust pH between 9.5 – 10.0. The reaction mixture was stirred for 1 hour at 25-30°Ctemperature. The product obtained was filtered

and washed with 2.5ml water. Dried the product at 55-60°C till constant weight. 6.0 g of R- (-)-5-(2-aminopropyl)-2-methoxybenzenesulfonamide was collected. Chiral purity: >99.9%;

Melting point: 166 °C – 167 °C.

$[\alpha]_D^{23}$: -17.31° (c = 1.07 , Methanol)

Dated this the 19th day of February 2004

H. SUBRAMANIAM
Of Subramaniam, Nataraj & Associates
Attorneys for the applicants